The influence of the molecular weight of the water-soluble polymer on phase-separated films for controlled release

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ABSTRACT

Hydroxypropyl cellulose (HPC) and ethyl cellulose (EC) can be used for extended release coatings, where the water-soluble HPC may act as a pore former. The aim was to investigate the effect of the molecular weight of HPC on the microstructure and mass transport in phase-separated freestanding EC/HPC films with 30% w/w HPC. Four different HPC grades were used, with weight averaged molecular weights (M_w) of 30.0 (SSL), 55.0 (SL), 83.5 (L) and 365 (M) kg/mol. Results showed that the phase-separated structure changed from HPC-discontinuous to bicontinuous with increasing M_w of HPC. The film with the lowest M_w HPC (SSL) had unconnected oval-shaped HPC-rich domains, leaked almost no HPC and had the lowest water permeability. The remaining higher M_w films had connected complex-shaped pores, which resulted in higher permeabilities. The highest M_w film (M) had the smallest pores and very slow HPC leakage, which led to a slow increase in permeability. Films with grade L and SL released most of their HPC, yet the permeability of the L film was three times higher due to greater pore connectivity. It was concluded that the phase-separated microstructure, the level of pore percolation and the leakage rate of HPC will be affected by the choice of HPC M_w grade used in the film and this will in turn have strong impact on the film permeability.

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1. Introduction

Coatings of polymer blends can be utilized to control drug release from pellets in pharmaceutical oral solid dosage forms. Mixing two polymers has several advantages compared to using only one polymer, not least additional possibilities to modify the coating by, for instance, changing the blend ratio (Siepmann et al., 2008) or using combinations of different polymer product grades (Rowe, 1986; Andersson et al., 2013). Coating properties that can be adjusted include e.g. the release rate and the mechanisms of drug release (Siepmann et al., 2008).

Ethyl cellulose (EC) and hydroxypropyl cellulose (HPC) are two cellulose derivatives that can be used in polymer blend coatings for extended release in oral pharmaceutics. These polymers differ in their solubility in water, i.e. pharmaceutically approved EC is normally insoluble, while HPC is soluble (Sakellariou and Rowe, 1995). In general, coherent films only composed of EC have low permeability to water (Lindstedt et al., 1989; Hjärtstam and Hjertberg, 1999a,b) and most drugs (Lecomte et al., 2003). For films of EC blends, however, the presence of a water-soluble polymer can lead to substantial polymer leakage during water exposure and formation of pores in the coating (Sakellariou et al., 1988), through which the drug can be released. Drug release is dependent on both

the extent of these formed pores as well as their shape (Marucci et al., 2009, 2010, 2011, 2013a; Andersson et al., 2013).

A thoroughly investigated method to regulate the extent of pores in mixed films is by changing the initial blend ratio of the soluble and insoluble polymer (Lindstedt et al., 1991; Marucci et al., 2009). This enables the modification of not only the release rate, but also the mechanism of drug release by shifting from a percolated to disconnected pore system (Marucci et al., 2009, 2010, 2011). Recent findings have, however, indicated that at a fixed blend ratio both the extent of pores as well as their shape can be modified by simply changing of the molecular weight grade of the coating polymer (Andersson et al., 2013; Marucci et al., 2013a). The origin of this effect is likely to stem from the implications of the molecular weight on the polymer phase separation, which occurs during manufacturing. To produce the aforementioned polymer blend films, the polymers must first be dissolved in a suitable common solvent. A solution consisting of EC, HPC and ethanol can be used for spray-coating EC/HPC blends on pellets (Marucci et al., 2010, 2011) or to produce freestanding films (Marucci et al., 2009; Larsson et al., 2010; Andersson et al., 2013; Marucci et al., 2013b), the latter being conveniently used as model systems for pellet coatings (Ye et al., 2007). Solvent evaporation during the spray-coating process is necessary for the formation of a solid film, but it also initiates segregative phase separation, leading to a film microstructure consisting of distinct domains enriched in either EC or HPC (Marucci et al., 2013b). During the progression of phase separation these domains grow until finally being arrested by a high solution viscosity. The HPC-rich phase in the final film microstructure can serve as a template for the pores mediating drug release, i.e. percolating pores form by leakage of HPC from the HPC-rich domains that are connected to both sides of the film during water exposure (Marucci et al., 2009). It has been shown that the phase-separated microstructure and resulting pore system depend on the blend ratio (Lindstedt et al., 1991; Marucci et al., 2009) and manufacturing conditions (Marucci et al., 2013b), but the molecular weight of EC can affect structure when the blend ratio and manufacturing conditions are kept the same (Andersson et al., 2013; Marucci et al., 2013a).

As of today, the effects of the molecular weight of EC on blended free films and pellets coatings have been studied (Rowe, 1986; Coppens et al., 2004; Dürig et al., 2005; Andersson et al., 2013; Marucci et al., 2013a) and it can be concluded that it has a significant impact on mass transport. However, the water-soluble component, HPC, in EC/HPC films is yet to be investigated. Varying the molecular weight of HPC adds an additional parameter to the dynamics of the film during water exposure, as the size of the leaking molecule will also be varied. The leakage rate of HPC is particularly important for pellet coatings, since the coating permeability for the drug can increase with the leakage of HPC (Marucci et al., 2013a). This study was aimed to investigate both structural features and mass transfer properties, including HPC leakage, of freestanding sprayed EC/HPC films with different molecular weight grades of HPC.

2. Materials and methods

2.1. Materials

HPC grades (Nisso HPC grade SSL, SL, L and M) were kindly supplied by Nippon Soda Co., Ltd., Japan. According to the manufacturers' product specifications the molecular weight of the HPC grades were in the range of 40 000 (SSL), 100 000 (SL), 140 000 (L) and 620 000 (M) g/mol, determined by gel permeation chromatography. The molar substitutions (MS) of the HPC grades were determined from the hydroxypropoxy (HPO) content of the

given HPC batches using the following formula:

$$HPO\%(w/w) = (100 \cdot 75 \cdot MS)/(58 \cdot MS + 162) \qquad (1)$$

The HPO-contents were given in the certificates of analysis (CoA) for the batches of HPC, supplied by the manufacturer.

EC (CR grade 10 cps) was from Dow Wolff Cellulosics, GmbH, Germany. The degree of substitution (DS) was calculated from the data in the CoA, supplied by the manufacturer, using the ethoxy (EtO) content and the following formula:

$$EtO\%(w/w) = (100 \cdot 45 \cdot DS)/(28 \cdot DS + 162) \qquad (2)$$

The radioactive tracer, [^{3}H]-water (37 MBq/g, 18 g/mol) and the scintillation cocktail (Ultima Gold Cocktail) used for permeability measurements were from Perkin Elmer Inc., USA. NaN$_3$ and NaCl used in the mobile phase were from Sigma Aldrich GmbH, Germany, and tetrahydrofuran (grade GPC) was from Fisher Chemicals (Switzerland). The pullulan standard Shodex STAN-DARD P-82 (Grade P-50, M$_w$ = 4.88·10^4) was from Showa Denko Europe GmbH, Germany. Ultra-pure deionized water was used in all experiments and hydrous ethanol (95% v/v Finsprit, Kemetyl AB, Sweden) was used for polymer dissolution.

2.2. Molecular weight determination

Size Exclusion Chromatography with multi-angle light scattering and refractive index detection (SEC-MALS/RI) was used to determine z-average molar mass (M$_z$), weight average molar mass (M$_w$) and number average molar mass (M$_n$) for EC and the different cellulose derivative grades of HPC. The polydispersity index (PI) was determined from the ratio of the weight and number averages, PI = M$_w$/M$_n$. The light sources used were at 690 nm and 658 nm for EC and HPC, respectively. The volume of each sample injection was 100 μl and the molecular weights were determined as averages of three injections.

EC was dissolved in the mobile phase (tetrahydrofuran) for at least 24 h prior to analysis and the sample concentration was 2.5 mg/ml. Details on the procedures can be found elsewhere (Andersson et al., 2013). HPC was dissolved in mobile phase, 10 mM NaCl, 0.02% w/v NaN$_3$, for at least 48 h prior to analysis. The sample concentrations used were 1 mg/ml (HPC SSL), 1 mg/ml (HPC SL), 0.7 mg/ml (HPC L) and 0.5 mg/ml (HPC M). The column was a TSKgel GMPWxl 7.8 mm D x 30.0 cm L, with a mean particle size of 13 μm (TOSOH Bioscience GmbH, Germany), the refractometer was an Optilab® T-rEX™ (Wyatt Technology, Santa Barbara, CA, USA) and the MALS instrument was a DAWN® HELEOS™ II (Wyatt Technology, Santa Barbara, CA, USA). The analyses were performed at 25 °C using a flow rate of 0.5 ml/min. A Waters 717plus Autosampler (Waters corporation, USA) with a 96-vial carousel was used and the vials used for the autoinjector were 700 μl Waters polypropylene 8 × 40 mm snap neck Total Recovery Vial supplied by Scantec Lab, Sweden. The refractive index increment (dn/dc) was set to 0.138 ml/g at and the software used to analyse the data was Astra 5.3.4.20 (Wyatt Technology, Santa Barbara, CA, USA) using a Berry linear model and exponential mass fitting. A pullulan standard (0.7 mg/ml) was set between every fifth or sixth sample to control the yield and accuracy of retention time.

2.3. Polymer solution preparation

All polymer solutions for film preparations were made by dissolving both EC and HPC in ethanol under vigorous magnetic stirring overnight. The EC/HPC polymer blend ratio was 70:30 (w/w). A useful method to be able to use comparable processing parameters during film and pellet coating manufacturing is to adjust the polymer content to obtain similar solution viscosities